MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to the olefinic derivatives of novel biphenyl 8-azoniabicyclo[3.2.1]octane compounds, pharmaceutical compositions, and use thereof in treating muscarinic acetylcholine receptor mediated diseases of the respiratory tract.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs where they mediate many of the vital functions. Muscarinic receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, M_3 mAChRs mediate contractile responses. For review, please see Caulfield (1993 *Pharmac. Ther.* **58**:319-79).

In the lungs, mAChRs have been localized to smooth muscle in the trachea and bronchi, the submucosal glands, and the parasympathetic ganglia. Muscarinic receptor density is greatest in parasympathetic ganglia and then decreases in density from the submucosal glands to tracheal and then bronchial smooth muscle. Muscarinic receptors are nearly absent from the alveoli. For review of mAChR expression and function in the lungs, please see Fryer and Jacoby (1998 *Am J Respir Crit Care Med* **158**(5, pt 3) S 154-60).

Three subtypes of mAChRs have been identified as important in the lungs, M_1, M_2 and M_3 mAChRs. The M_3 mAChRs, located on airway smooth muscle, mediate muscle contraction. Stimulation of M_3 mAChRs activates the enzyme phospholipase C via binding of the stimulatory G protein Gq/11 (Gs), leading to

liberation of phosphatidyl inositol-4,5-bisphosphate, resulting in phosphorylation of contractile proteins. M_3 mAChRs are also found on pulmonary submucosal glands. Stimulation of this population of M_3 mAChRs results in mucus secretion.

M_2 mAChRs make up approximately 50-80% of the cholinergic receptor population on airway smooth muscles. Although the precise function is still unknown, they inhibit catecholaminergic relaxation of airway smooth muscle via inhibition of cAMP generation. Neuronal M_2 mAChRs are located on postganglionic parasympathetic nerves. Under normal physiologic conditions, neuronal M_2 mAChRs provide tight control of acetylcholine release from parasympathetic nerves. Inhibitory M_2 mAChRs have also been demonstrated on sympathetic nerves in the lungs of some species. These receptors inhibit release of noradrenaline, thus decreasing sympathetic input to the lungs.

M_1 mAChRs are found in the pulmonary parasympathetic ganglia where they function to enhance neurotransmission. These receptors have also been localized to the peripheral lung parenchyma, however their function in the parenchyma is unknown.

Muscarinic acetylcholine receptor dysfunction in the lungs has been noted in a variety of different pathophysiological states. In particular, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation (Fryer et al. 1999 *Life Sci* **64** (6-7) 449-55). This mAChR dysfunction results in airway hyperreactivity and hyperresponsiveness mediated by increased stimulation of M_3 mAChRs. Thus the identification of potent mAChR antagonists would be useful as therapeutics in these mAChR-mediated disease states.

COPD is an imprecise term that encompasses a variety of progressive health problems including chronic bronchitis, chronic bronchiolitis and emphysema, and it is a major cause of mortality and morbidity in the world. Smoking is the major risk factor for the development of COPD; nearly 50 million people in the U.S. alone smoke cigarettes, and an estimated 3,000 people take up the habit daily. As a result, COPD is expected to rank among the top five as a world-wide health burden by the

year 2020. Inhaled anti-cholinergic therapy is currently considered the "gold standard" as first line therapy for COPD (Pauwels et al. 2001 *Am. J. Respir. Crit. Care Med.* **163**:1256-1276).

Despite the large body of evidence supporting the use of anti-cholinergic therapy for the treatment of airway hyperreactive diseases, relatively few anti-cholinergic compounds are available for use in the clinic for pulmonary indications. More specifically, in United States, Ipratropium Bromide (Atrovent©; and Combivent©, in combination with albuterol) is currently the only inhaled anti-cholinergic marketed for the treatment of airway hyperreactive diseases. While this compound is a potent anti-muscarinic agent, it is short acting, and thus must be administered as many as four times daily in order to provide relief for the COPD patient. In Europe and Asia, the long-acting anti-cholinergic Tiotropium Bromide (Spiriva©) was recently approved, however this product is currently not available in the United States. Thus, there remains a need for novel compounds that are capable of causing blockade at mAChRs which are long acting and can be administered once-daily for the treatment of airway hyperreactive diseases such as asthma and COPD.

Since mAChRs are widely distributed throughout the body, the ability to apply anti-cholinergics locally and/or topically to the respiratory tract is particularly advantageous, as it would allow for lower doses of the drug to be utilized. Furthermore, the ability to design topically active drugs that have long duration of action, and in particular, are retained either at the receptor or by the lung, would allow the avoidance of unwanted side effects that may be seen with systemic anti-cholinergic use.

SUMMARY OF THE INVENTION

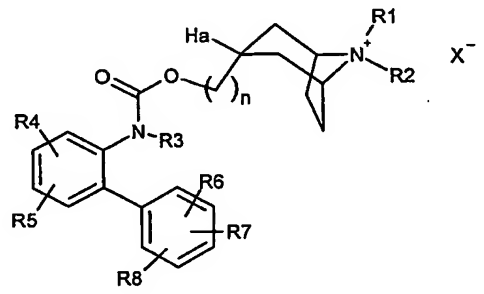
This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an mAChR and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises

administering to aforementioned mammal an effective amount of a compound of Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) useful in the present invention are represented by the structure:



(I)

wherein:

n is 0 or 1;

Ha is an hydrogen atom in the exo postion,

R1 and R2 are, independently, selected from the group consisting of a bond, hydrogen and methyl;

R3 is selected from the group consisting of hydrogen and C1-4 alkyl;

R4 and R5 are independently selected from the group consisting of hydrogen, halogen, C1-4 alkyl, C2-4 alkenyl, halo substituted C1-4 alkyl, (CR9R9)qORa, hydroxy substituted C1-4 alkyl, and (CR9R9)qNC(O)Ra

R6, R7 and R8 are, independently, selected from the group consisting of hydrogen, halogen, cyano, C1-4 alkyl, C2-4 alkenyl, C1-4 alkoxy, halo-substituted C1-4 alkyl, (CR9R9)qORa, hydroxy substituted C1-4 alkyl, and (CR9R9)qNC(O)Ra; or two of either R6, R7 or R8 moieties together may form a 5 to 6 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroalkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

Ra is selected form the group consisting of hydrogen, C1-4 alkyl, and halo substituted C1-4 alkyl;

R9 is hydrogen or C1-4 alkyl

q is 0, or an integer having a value of 1 to 4;

X- is a physiologically acceptable anion, such as chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate and p-toluenesulfonate.

All of the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted as defined herein below.

For use herein the term "the aryl, heteroaryl, and heterocyclic containing moieties" refers to both the ring and the alkyl, or if included, the alkenyl rings, such as aryl, arylalkyl, and aryl alkenyl rings. The term "moieties" and "rings" may be interchangeably used throughout.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_{m'}$ C_{1-10} alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the $NR_{10}R_{11}$ group; $NHC(O)R_9$; $C(O)NR_{10}R_{11}$; C(O)OH; $S(O)_2NR_{10}R_{11}$; $NHS(O)_2R_9$, C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl,

optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl , heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_{m'}C_{1-10}$ alkyl; amino, mono & di-substituted alkyl amino, such as in the $NR_{10}R_{11}$ group; C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl, such as CF_3.

The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or

imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

• "wherein two R_1 moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of an aromatic ring system, such as naphthalene, or is a phenyl moiety having attached a 6 membered partially saturated or unsaturated ring such as a C_6 cycloalkenyl, i.e. hexene, or a C_5 cycloalkenyl moiety, such as cyclopentene.

Illustrative compounds of the present invention include Examples 1 through 140, disclosed on pages 24 – 62 of the specification hereinafter.

Preferred compounds of Formula (I) include:

(3-*endo*)-3-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-3-[({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-3-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl 2-biphenylylcarbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-hydroxy-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-6-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-fluoro-2-biphenylyl)carbamate;
(3-*endo*)-3-[({[(3'-chloro-5-hydroxy-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;
(3-*endo*)-3-[({[(3'-chloro-4-fluoro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-methyl-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-fluoro-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-3'-methyl-2-biphenylyl)carbamate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',5-difluoro-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4,4'-difluoro-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4',5-difluoro-2-biphenylyl)carbamate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-2-biphenylyl)carbamate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-2-biphenylyl)carbamate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',5-difluoro-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4',5-difluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-2-biphenylyl)carbamate;
(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (5-fluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate;
(3-*endo*)-3-[({[(3'-chloro-3-methyl-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-3-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-methyl-2-biphenylyl)carbamate;

(3-*endo*)-3-[({[(3'-chloro-6-fluoro-2-biphenylyl)(methyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-5-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-methyl-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4',6-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (6-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',4-dichloro-4'-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-3-({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-3,4'-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4'-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4',5-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3',5-dichloro-4'-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4',6-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-3-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4',5-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-5-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3',5-dichloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-3,4'-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-6-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4',6-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3',5-dichloro-4'-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-{[(2-biphenylylamino)carbonyl]oxy}-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4'-fluoro-4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3',4-dichloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(5-chloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8,8-dimethyl-3-({[(4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (5-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-6-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-3-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide; and

(3-*endo*)-3-({[(6-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

More preferred compounds Formula (I) useful in the present invention include:

(3-*endo*)-3-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-3-[({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-3-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl 2-biphenylylcarbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-hydroxy-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-6-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-[({[(3'-chloro-5-hydroxy-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-3-[({[(3'-chloro-4-fluoro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-3'-methyl-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',5-difluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4,4'-difluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4',5-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',5-difluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4',5-difluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (5-fluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-3-({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-3,4'-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4'-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4',5-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3',5-dichloro-4'-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4',6-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-3-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4',5-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-5-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3',5-dichloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-3,4'-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-6-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4',6-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3',5-dichloro-4'-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-{[(2-biphenylylamino)carbonyl]oxy}-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4'-fluoro-4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3-fluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3',4-dichloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(5-chloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8,8-dimethyl-3-({[(4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (5-fluoro-2-biphenylyl)carbamate; and

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-6-fluoro-2-biphenylyl)carbamate.

Even more preferred compounds Formula (I) useful in the present invention include:

(3-*endo*)-3-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-3-[({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-3-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl 2-biphenylylcarbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-hydroxy-2-biphenylyl)carbamate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-methyl-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-6-fluoro-2-biphenylyl)carbamate trifluoroacetate;

(3-*endo*)-3-({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-3,4'-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4'-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4',5-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3',5-dichloro-4'-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-4',6-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-({[(3'-chloro-3-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4',5-difluoro-2-biphenylyl)carbamate;

(3-*endo*)-3-({[(3'-chloro-5-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

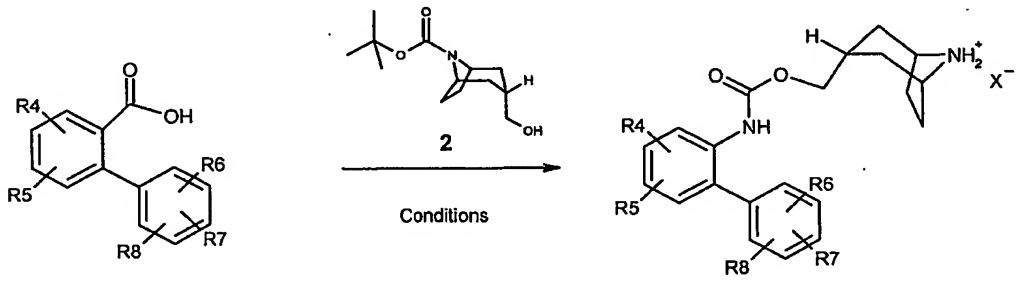
(3-*endo*)-3-({[(3',5-dichloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-3,4'-difluoro-2-biphenylyl)carbamate;
(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-2-biphenylyl)carbamate;
(3-*endo*)-3-({[(3'-chloro-6-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4',6-difluoro-2-biphenylyl)carbamate;
(3-*endo*)-3-({[(3-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3',5-dichloro-4'-fluoro-2-biphenylyl)carbamate;
(3-*endo*)-3-({[(3'-chloro-4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-*endo*)-3-{[(2-biphenylylamino)carbonyl]oxy}-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-*endo*)-3-({[(3'-chloro-4'-fluoro-4-methyl-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide; and
(3-*endo*)-3-({[(5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide.

Particularly preferred compounds of the present invention include:
(3-endo)-3-({[(3'-chloro-4',5-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide; and
3-endo)-3-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate.

METHODS OF PREPARATION

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis

provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R_x groups (X=1 to 7) which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While the Schemes are shown with compounds only of Formula (I), this is merely for illustration purpose only.



1 (I, R1=R2=H)

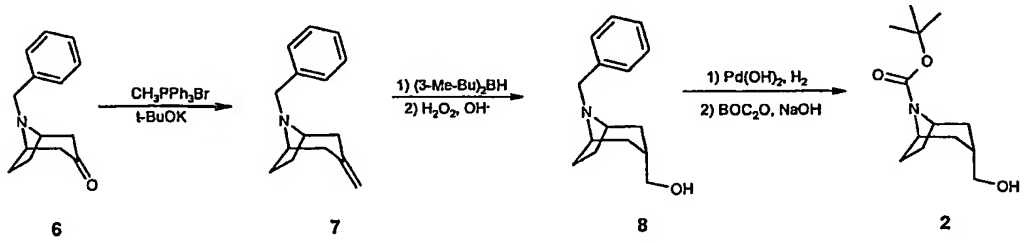
Reagents and conditions: a) Diphenylphosphoryl azide, triethylamine, $CHCl_3$; b) HX, solvent

Scheme 1

As outlined in Scheme 1, the desired compounds of Formula (I) can be prepared via the Curtius reaction of a suitable biphenyl acid **1** with the suitably protected [3.2.1] bicyclic alcohol **2** using standard reagents well known in the art such as the commercially available diphenylphosphoryl azide (DPPA) reagent. Removal of the protecting group using standard conditions such as treatment with *p*-toluenesulfonic acid in acetonitrile gives the compound of Formula (I).

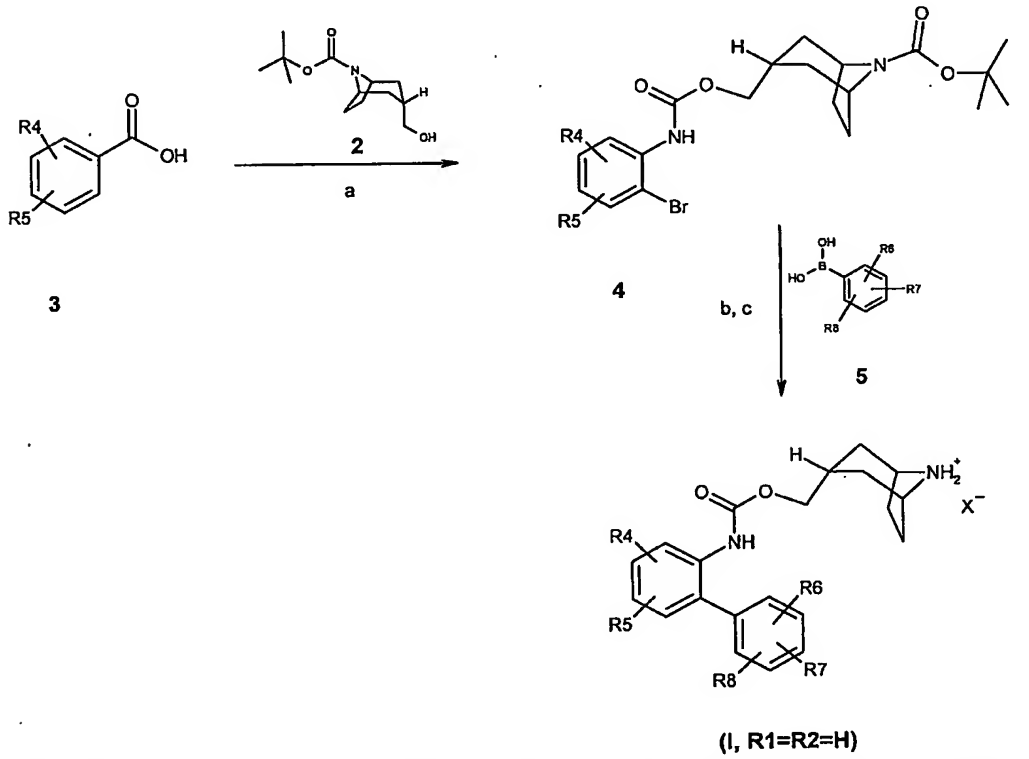
The required [3.2.1] bicyclic alcohol **2** is not commercially available but can be prepared from compound **6** which has been previously described in the literature (T. Momone *et al*, *J.C.S. Perkin. Trans. 1*, **9**, 1997, 1307-14). As shown in Scheme 2, compound **7** was prepared by the Wittig reaction of compound **6** using standard reagents such as methyltriphenyl phosphonium bromide and potassium *tert*-butoxide. Hydroboration of alkene **7** with disiamylborane followed by oxidation produced the alcohol **8**. Subsequent removal of the benzylic moiety of **8** under hydrogenation conditions followed by protection of the ring nitrogen with a BOC

group using standard conditions such as treatment with di-*tert*-butyl dicarbonate in the presence of a base such as sodium hydroxide gave the desired alcohol **2**.



Scheme 2

Alternatively, if the suitable bi-phenyl acid **1** is not commercially available, the desired compounds of Formula (I) can also be prepared as outlined in Scheme 3.

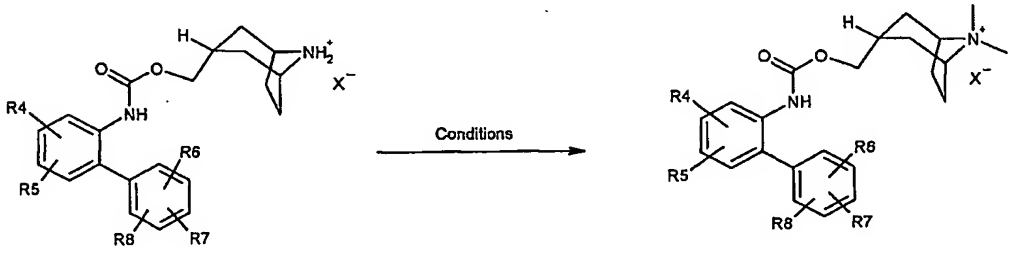


Reagents and conditions: a) Diphenylphosphoryl azide, triethylamine, b) Pd(Ph)4, base, DMF/H2O c) HX, solvent

Scheme 3

A suitable carboxylic acid **3** can be reacted with the suitably protected [3.2.1] bicyclic alcohol **2** via the Curtius reaction using standard reagents well known in the art such as the commercially available diphenylphosphoryl azide (DPPA) reagent. The intermediate **4** thus formed can be coupled to a suitable boronic acid **5** using standard methods well known in the art such as the Suzuki coupling with catalytic tetrakis(triphenylphosphino)palladium (0) in dimethylformamide and water in a presence of a base such as sodium carbonate or triethylamine. Removal of the protecting group on **4** using standard conditions such as treatment with *p*-toluenesulfonic acid in acetonitrile gives the compound of Formula (I).

As outlined in scheme 4, in the case where the compound of general formula (I) is a dimethyl quaternary salt (R1 and R2 = CH_3), it may be prepared by reacting the corresponding secondary amine (I, R1=R2=H) with a suitable alkylating reagent such as methyl bromide or methyl iodide with a base such as potassium carbonate in an inert solvent such as dimethylformamide.

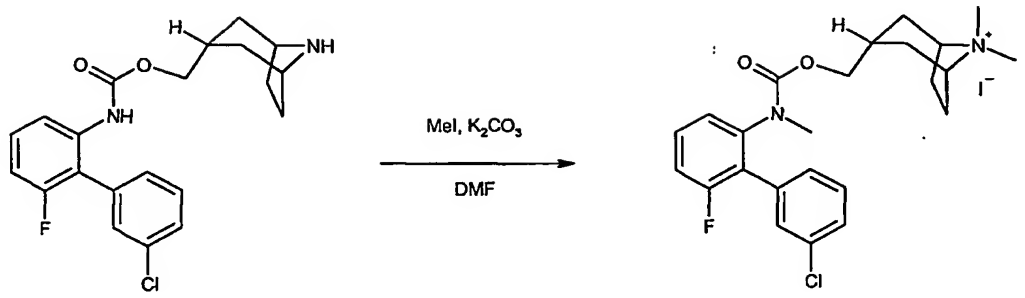


(I, R1=R2=H) (I, R1 and R2 =CH_3)

Reagents and conditions: MeBBr or MeI, K_2CO_3, DMF.

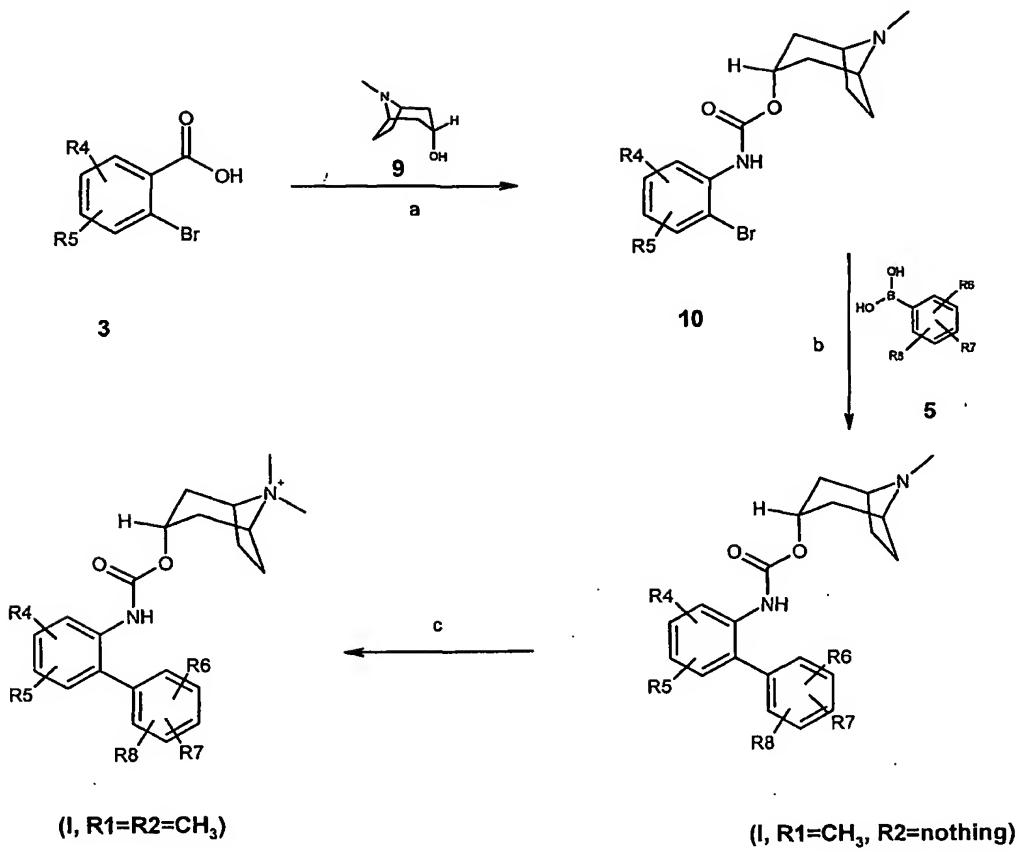
Scheme 4

In some cases, alkylation of the carbonate nitrogen may also occur. A representative example is shown in Scheme 5.



Scheme 5

The compounds of general formula (I) may also be prepared as depicted in Scheme 6. A suitable carboxylic acid **3** can be reacted with the commercially available bicyclic alcohol **9** via the Curtius reaction using standard reagents well known in the art such as the commercially available diphenylphosphoryl azide (DPPA) reagent. The intermediate **10** thus formed can be coupled to a suitable boronic acid **5** using standard methods well known in the art such as the Suzuki coupling with polymer supported (triphenylphosphino)palladium(0) in DME and water in a presence of a base such as potassium carbonate to give the compound of Formula (I) (R1=CH_3, R2=nothing). Reacting this compound with a suitable methylating agent such as methyl iodide or methyl bromide leads to the corresponding dimethyl quaternary salt of Formula (I) (R1=R2=CH_3).



Reagents and conditions: a) Diphenylphosphoryl azide, triethylamine, b) PS-Ph_3-Pd, base, DME/H_2O c) MeBr or MeI, DCM/Acetonitrile

Scheme 6

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following Examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. Most reagents and intermediates are commercially available or are prepared according to procedures in the literature. The preparation of intermediates not described in the literature is illustrated below. Flash column chromatography was carried out using Merck 9385 silica unless stated otherwise. LC/MS analyses were conducted under the following conditions:

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS

- Flow Rate: 3ml/min
- Injection Volume: 5µl
- Temp: Room temperature
- Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
  B: 95% Acetonitrile + 0.05% Formic Acid
- Gradient:

Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

The Mass Directed Automated Preparative (MDAP) was conducted under the conditions described in System A or in System B:

System A: Formate salts

- The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5m)
- UV detection wavelength : 200-320nM
- Flow rate : 20ml/min
- Injection Volume: 0.5ml
- Solvent A : 0.1% formic acid
- Solvent B : 95% acetonitrile + 0.05% formic acid

System B TFA salts

- The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5m)
- UV detection wavelength : 200-320nM
- Flow rate : 20ml/min

- Injection Volume: 0.5ml
- Solvent A : water + 0.1% trifluoroacetic acid
- Solvent B : acetonitrile + 0.1% trifluoroacetic acid

The Gilson preparatory HPLC was conducted under the following conditions:

- Column: 75 x 33mm I. D. , S-5um, 12nm
- Flow rate: 30mL/min
- Injection Volume: 0.800 mL
- Room temperature
- Solvent A: 0.1% trifluoroacetic acid in water
- Solvent B: 0.1% trifluoroacetic acid in acetonitrile

The following examples are intended to be illustrative of the present invention but not limiting in any way.

Preparation of 1,1-dimethylethyl -(3-*endo*)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step a: Preparation of 3-methylidene-8-(phenylmethyl)-8-azabicyclo[3.2.1]octane

A 500 ml flask with side arm, stirring bar, N_2 inlet, and septum stopper was charged with a solution of potassium *tert*-butoxide in THF (82 ml, 1M) and methyltriphenyl phosphonium bromide (29.2 g, 82 mmol). It was cooled to 0 °C under dry N_2, and anhydrous THF (140 ml) was added *via* syringe at 0 °C. The ylid solution was stirred for 20 min. 8-(Phenylmethyl)-8-azabicyclo[3.2.1]octan-3-one (14.0 g, 65 mmol) in anhydrous THF (ml) was added *via* syringe at 0 °C and the solution was stirred 1 h at room temperature then quenched with water (6 ml). The mixture was acidified to pH 1 and THF was removed *in vacuo* at 30 °C. The residue was diluted with water (450 ml) and Ph_3PO was extracted with toluene (3 X 200 ml). The aqueous solution was basified with 6N NaOH (~35 ml), and extracted with ethyl acetate (3 X 200ml). The organic layers were combined, washed with saturated NaCl (3 X 100 ml), dried over Na_2SO_4, and evaporated to yield a crude product

which was purified by flash chromatography (400g of silica, ethyl acetate containing 0.1% TEA). 3-Methylidene-8-(phenylmethyl)-8-azabicyclo[3.2.1]octane was recovered as a yellow oil (11.3 g, 81.5 %). LC/MS ESI R_t 1.27 min, MH+ 214; NMR ($CDCl_3$, 400MHz; δ): 1.58 ppm (q, 2H), 1.80-2.05 ppm (m, 4H), 2.55 ppm (d, 2H), 3.28 ppm (s, 2H), 3.65 ppm (s, 2H), 4.80 ppm (s, 2H), 7.29 ppm (t, 1H), 7.35 ppm (t, 2H), 7.46 ppm (d, 2H).

Step b: Preparation of (3-*endo*)-8-(phenylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]methanol

A solution of disiamylborane was prepared by addition of 1.0 M borane in THF (20 ml, 20 mmol) to a 2.0 M solution of 2-methyl-2-butene in THF (20 ml, 40 mmol) at 0 °C under N_2. The solution was stirred 1 h at 0 °C before addition of 3-methylidene-8-(phenylmethyl)-8-azabicyclo[3.2.1]octane (1.07 g, 5 mmol) in 10 ml anhydrous THF. After 0.5 h at 0 °C the reaction mixture was warmed up to room temperature and allowed to stir overnight. The borane was quenched by *careful* addition of water (2 ml). The stirred solution was then oxidized at 0 °C by adding dropwise an aqueous solution of 30 % H_2O_2 (3.87 ml, 45 mmol) over 30 minutes. The reaction mixture was neutralized with 3N HCl and the solvent was evaporated. The residue was taken up in ethyl acetate. Evaporation gave a viscous crude oil which was used directly for step c.

Step c: Removal of the benzyl group and protection with a BOC group

A solution of (3-*endo*)-8-(phenylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]methanol (1.16 g) (Schneider *et al*, *Arch. Pharm.*, 1975, 308-365) in ethanol (20 ml) and 6N HCl (1 ml) containing palladium hydroxide on carbon (Pearlman's catalyst, 2.27 g, 22% (w/w)) was hydrogenated (55 psi H_2) at room temperature for 2 days. The catalyst was filtered off over Celite and the filtrate was evaporated under vacuum. The residue and di-*tert*-butyl dicarbonate (1.63 g, 7.5 mmol) were dissolved in 30 ml of dioxane:1 N NaOH (2:1) and stirred overnight at room temperature. The solvent was evaporated and the residue partitioned between ethyl acetate (3 X 25 ml)and water (25 ml). The combined organic layers were dried over Na_2SO_4 and

evaporated. The residue oil was purified by flash chromatography (150g of silica, hexane:ethyl acetate (1:1, containing 0.1% 2.0 M NH_3 in methanol)). A colorless oil (0.65 g) was obtained. LC/MS ESI RT 1.65 min, MH+ 242. NMR ($CDCl_3$, 400MHz; δ) 4.15 ppm (broad, 2H), 3.64 ppm (d, 2H), 2.20 ppm (broad, 2H),1.97 ppm (broad, 2H), 1.85 ppm (m, 1H), 1.60 ppm (m, 2H), 1.40-1.50 ppm (s+broad, 11H).

Intermediate 1: 1,1-Dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

A solution of 2-bromo-5-methylbenzoic acid (430mg) in chloroform (10ml) was treated with diphenylphosphoryl azide (450 µl) and triethylamine (450 µl). The resulting reaction mixture was heated at 60°C for 10 minutes then treated with a solution of 1,1-dimethylethyl -(3-*endo*)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (470mg) in chloroform (2ml). The reaction mixture was heated at reflux for 6 hours. The cooled solution was loaded onto a SPE cartridge (Si, 10g). Elution with chloroform, followed by evaporation of the solvent gives the title compound (920mg). LC/MS ESI R_T 3.93 mins MH^+ 453.

Intermediate 2: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromobenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.79 mins MH^+ 439.

Intermediate 3: 1,1-dimethylethyl (3-*endo*)-{[({[2-bromo-3,4-bis(methyloxy)phenyl]amino}carbonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-3,4-bis(methyloxy)benzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.63 mins MH^+ 499 .

Intermediate 4: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-5-chlorobenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 4.05 mins MH^+ 473.

Intermediate 5: 1,1-dimethylethyl (3-*endo*)-{[({[2-bromo-5-(methyloxy)phenyl]amino}carbonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-5-(methyloxy)benzoic acid using the procedure described for the preparation of intermediate 1. NMR (d^6-DMSO 400MHz; δ) 7.84 (br, 1H), 7.46-7.35 (m,1H), 7.18-7.11 (m,1H), 6.56-6.51 (m,1H), 4.33-4.10 (m's,4H), 3.81 (s,3H), 2.31-1.95 (m's,5H), 1.74-1.64 (m,2H), 1.5-1.41 (m's, 11H)

Intermediate 6: 1,1-dimethylethyl (3-*endo*)-{[({[5-(acetylamino)-2-bromophenyl]amino}carbonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 5-(acetylamino)-2-bromobenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.49 mins MH^+ 496 .

Intermediate 7: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-4-methylbenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.91 mins MH^+ 453 .

Intermediate 8: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-6-methylbenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.64 mins MH^+ 453 .

Intermediate 9: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-5-fluorobenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.92 mins MH^+ 457 .

Intermediate 10: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-3-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-3-fluorobenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.83 mins MH^+ 457 .

Intermediate 11: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-4-fluorobenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.78 mins MH^+ 457 .

Intermediate 12: methyl 3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylcarboxylate

Nitrogen was bubbled slowly through a stirred mixture of dioxane (3ml), cesium carbonate (600mg) 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (8.5mg) and

palladium acetate (5.5mg) for 5 minutes. A mixture of methyl 4-[(phenylmethyl)oxy]-2-{[(trifluoromethyl)sulfonyl]oxy}benzoate (390mg) and 3-chloroboronic acid (231mg) were added and the vessel was sealed. The resulting mixture was heated in a microwave (Smith Creator, 150°C, 10 minutes). After cooling, the reaction mixture was diluted with dichloromethane (5ml), filtered through Hyflo and evaporated. The residue was purified by chromatography (20g Si, Flashmaster2) eluting with ethyl acetate/cyclohexane (2:98). The title compound was recovered as a white solid (280mg). LC/MS ESI R_T 3.88 mins MH^+ 353.

Intermediate 13: 3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylcarboxylic acid

A mixture of methyl 3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylcarboxylate , methanol (5ml), tetrahydrofuran (5ml) and 2N sodium hydroxide (3ml) was heated at 60°C for 2 hours. The cooled solution was added to 2N hydochloric acid (50ml) and extracted with dichloromethane (3x50ml),. The organic fractions were combined, dried ($MgSO_4$) and evaporated to give the title compound as a white powder (380mg). LC/MS ESI R_T 3.74 mins MH^+ 339 .

Intermediate 14: 1,1-dimethylethyl (3-*endo*)-({[({3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylyl}amino)carbonyl]oxy}methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylcarboxylic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 4.09 mins MH^+ 577 .

Intermediate 15: 1,1-dimethylethyl (3-*endo*)-[({[(3'-chloro-5-hydroxy-2-biphenylyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of palladium acetate (6mg), triethylamine (11 µl) and triethylsilane (125 µl) in dichloromethane (2ml) was stirred for 5 minutes to give a black suspension. A solution of 1,1-dimethylethyl (3-*endo*)-({[({3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylyl}amino)carbonyl]oxy}methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (280 mg) in dichloromethane was added dropwise and the resulting reaction mixture

was stirred for 16 hours. Further palladium acetate (6mg), triethylamine (11 µl) and triethylsilane (125 µl) were added and further stirring continued for 24 hours. The mixture was treated with aqueous ammonium chloride (5ml) and extracted with dichloromethane (2x5ml). The combined organic fractions were evaporated and the residue was dissolved in tetrahydrofuran (2ml) then treated with a 1M solution of tetrabutylammonium fluoride in THF (1ml). The resulting solution was stirred for 1 hour, the solvent was removed under vacuum to give a residue which was diluted with cyclohexane then loaded onto a SPE cartridge (Si 20g). Elution with a mixture cylcoheaxne/diethyl ether gives the title compound (180mg).

NMR (d^6-DMSO 400MHz; δ) 7.84-7.65 (br,1H), 7.51-7.21 (m's, 3H), 7.26-7.21 (m, 1H, excess), 6.87-6.81 (m,1H), 6.76-6.71 (m,1H), 6.39-6.15 (br m,1H), 5.16 (br,1H), 4.29-4.01 (m's,4H), 2.20-1.26 (m's,18H, excess).

Intermediate 16: 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

The title compound was prepared from 2-bromo-6-fluorobenzoic acid using the procedure described for the preparation of intermediate 1. LC/MS ESI R_T 3.45 mins MH^+ 457 .

Example 1: (3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl [3'-(trifluoromethyl)-2-biphenylyl]carbamate

A solution of 3'-(trifluoromethyl)-2-biphenylcarboxylic acid (0.05 mmol) in chloroform (0.5ml) was successively treated with a solution of diphenylphosphoryl azide (11µl) in chloroform (0.2ml) then a solution of triethylamine (11µl) in chloroform (0.2ml). The resulting solution was maintained at 50°C for 10 minutes then treated with a solution of 1,1-dimethylethyl -(3-*endo*)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (12mg) in chloroform (0.2ml). After heating at reflux for 16 hours, the cooled solution was purified by loading onto a SPE cartridge (NH_2, 500mg) then eluting with chloroform. After removing the solvent under vacuum, the residue was dissolved in acetonitrile (0.5ml), treated with a solution of *p*-toluenesulfonic acid (10mg) in acetonitrile (0.5ml) and the resulting

mixture was heated at reflux for 3 hours. The cooled solution was purified by loading onto a SPE cartridge (SCX, 500mg) then washing with methanol and eluting with 2M ammonia in methanol to give the title compound. LC/MS ESI R_T 2.33 mins MH^+ 405.

Example 2: (3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl[4-fluoro-4'-(trifluoromethyl)-2-biphenylyl]carbamate

The title compound was prepared from 4-fluoro-4'-(trifluoromethyl)-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.43 mins MH^+ 423.

Example 3: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl-3',4'-bis(methyloxy)-2-biphenylyl]carbamate.

The title compound was prepared from 4'-methyl-3'-(methyloxy)-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.12 mins MH^+ 397.

Example 4: (3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl (4'-butyl-2-biphenylyl)carbamate

The title compound was prepared from 4'-butyl-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.58 mins MH^+ 393.

Example 5: (3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl[5-chloro-4'-(trifluoromethyl)-2-biphenylyl]carbamate

The title compound was prepared from 5-chloro-4'-(trifluoromethyl)-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.52 mins MH^+ 439.

Example 6: (3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl[6-chloro-4'-(trifluoromethyl)-2-biphenylyl]carbamate

The title compound was prepared from 6-chloro-4'-(trifluoromethyl)-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.48 mins MH^+ 439.

Example 7: (3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl (2'-methyl-2-biphenylyl)carbamate

The title compound was prepared from 2'-methyl-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.26 mins MH^+ 351.

Example 8: (3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl (4'-hydroxy-2-biphenylyl)carbamate

The title compound was prepared from 4'-hydroxy-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.04 mins MH^+ 353.

Example 9: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [4'-(trifluoromethyl)-2-biphenylyl]carbamate

The title compound was prepared from 4'-(trifluoromethyl)-2-biphenylcarboxylic acid according to the procedure outlined in example 1. LC/MS ESI R_T 2.35 mins MH^+ 405.

Example 10: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-methyl-2-biphenylyl)carbamate trifluoroacetate

A solution of (3-*endo*)-[({[(2-bromo-5methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (45 mg) and (3-chlorophenyl)boronic acid (23.4 mg) in dimethylformamide (0.75ml) was treated with sodium carbonate (30mg), tetrakis(triphenylphosphino)palladium (0) (58 mg) and water (0.25ml). The mixture was placed in a sealed reaction tube and heated in a microwave (CEM Explorer, 150°C, 10 minutes, pressure 250psi, power 100W). After cooling to room

temperature, the solvent was removed under vacuum. The residue was dissolved in chloroform (1ml) then washed sequentially with 2N hydrochloric acid (0.5ml) and water (0.5ml). The organic phase was separated and the solvent was removed under vacuum. The residue was dissolved in acetonitrile (1 ml) and treated with *p*-toluenesulfonic acid (20mg) . The resulting mixture was heated at reflux for 3 hours. After cooling to room temperature, the solution was purified by loading onto a SPE cartridge (SCX, 500mg) then washing with methanol and eluting with 2M ammonia in methanol. The solvent was removed under vacuum and the residue was purified by MDAP to afford the title compound. LC/MS ESI R_T 2.57 mins MH^+ 385.

Example 11: (3-*endo*)-3-({[({3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylyl}amino)carbonyl]oxy}methyl)-8-azoniabicyclo[3.2.1]octane 4-methylbenzenesulfonate

A solution of 1,1-dimethylethyl (3-*endo*)-({[({3'-chloro-5-[(phenylmethyl)oxy]-2-biphenylyl}amino)carbonyl]oxy}methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (11mg) and *p*-toluenesulfonic acid (12mg) in chloroform (0.5ml) was heated in a microwave (Smith Creator, 100°C, 7 minutes). After cooling to room temperature, the solvent was removed under vacuum. The resulting residue was purified by flash tube after elution with DCM/MeOH/NH3 (75:25:2) to give the title compound (7 mg) as its p-toluene sulfonate salt. NMR (d^6-DMSO 400MHz; δ) 7.80-7.65 (m, 2H), 7.49-7.13 (m's,13H, excess), 7.05-6.94 (m, 1H), 6.91-6.85 (m,1H), 5.07 (s,2H), 4.15-3.90 (m's,4H), 2.36 (s,3H), 2.31-2.08 (m's,5H), 1.96-1.80 (m, 2H), 1.68-1.53 (m,2H).

Example 12: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-hydroxy-2-biphenylyl)carbamate

A solution of 1,1-dimethylethyl (3-endo)-[({[(3'-chloro-5-hydroxy-2-biphenylyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (11mg) and p-toluenesulfonic acid (12mg) in chloroform (0.5ml) was heated in a microwave (Smith Creator, 100°C,7 minutes). After cooling to room temperature,

the solvent was removed under vacuum. The resulting residue was purified by MDAP to give the title compound (2.5mg). LC/MS ESI R_T 2.25 mins MH^+ 387.

Example 13: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',4'-dichloro-2-biphenylyl)carbamate

A solution of 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (44 mg) and (2,4-dichlorophenyl)boronic acid (28 mg) in dimethylformamide (0.75ml) was treated with sodium carbonate (30mg), tetrakis(triphenylphosphino)palladium (0) (35 mg) and water (0.25ml). The mixture was placed in a sealed reaction tube and heated in a microwave (CEM Explorer, 150°C, 10 minutes, pressure 250psi, power 100W). After cooling to room temperature, the solvent was removed under vacuum. The residue was dissolved in chloroform (1ml) then washed sequentially with 2N hydrochloric acid (0.5ml) and water (0.5ml). The organic phase was separated and the solvent was removed under vacuum. The residue was dissolved in acetonitrile (1 ml) and treated with *p*-toluenesulfonic acid (20mg) . The resulting mixture was heated at reflux for 3 hours. After cooling to room temperature, the solution was purified by loading onto a SPE cartridge (SCX, 500mg) then washing with methanol and eluting with 2M ammonia in methanol. The solvent was removed under vacuum and the residue was purified by MDAP to afford the title compound (20mg). LC/MS ESI R_T 2.6 mins MH^+ 379.

Example 14: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',4',6'-trimethyl-2-biphenylyl)carbamate

According to the procedure outlined in example 13, (2,4,6-trimethylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 1.9 mins MH^+ 380.

Example 15: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',3'-dimethyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (2,3-dimethylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.47 mins MH^+ 365.

Example 16: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',5'-dimethyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, 2,5-dimethylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.49 mins MH^+ 365.

Example 17: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-3'-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (4-fluoro-3-methylphenyl)boronic and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.4 mins MH^+ 369.

Example 18: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-2'-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (4-fluoro-2-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.41 mins MH^+ 369.

Example 19: (3-endo)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-ethyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (4-ethylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-

azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI RT 2.48 mins MH+ 365.

Example 20: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [2-(2-naphthalenyl)phenyl]carbamate

According to the procedure outlined in example 10, 2-naphthalenylboronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI RT 2.50 mins MH+ 387.

Example 21: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.28 mins MH^+ 355.

Example 22: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl {3'-[(trifluoromethyl)oxy]-2-biphenylyl}carbamate

According to the procedure outlined in example 10, {3-[(trifluoromethyl)oxy]phenyl}boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.52 mins MH^+ 421.

Example 23: (3-endo)-8-azabicyclo[3.2.1]oct-3-ylmethyl {3'-[(methyloxy)methyl]-2-biphenylyl}carbamate

According to the procedure outlined in example 10, {3-[(methyloxy)methyl]phenyl}boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.27 mins MH^+ 381.

Example 24: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (2-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.24 mins MH^+ 355.

Example 25: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [2'-(trifluoromethyl)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, (2-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.45 mins MH^+ 405.

Example 26: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [4'-(1,1-dimethylethyl)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, [4-(1,1-dimethylethyl)phenyl]boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.65 mins MH^+ 393.

Example 27: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl 1,1':4',1''-terphenyl-2-ylcarbamate

According to the procedure outlined in example 10, 4-biphenylylboronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.64 mins MH^+ 413.

Example 28: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',3'-difluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (2,3-difluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-

bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.29 mins MH^+ 373.

Example 29: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.38 mins MH^+ 351.

Example 30: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.37 mins MH^+ 351.

Example 31: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-fluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.28 mins MH^+ 355.

Example 32: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-4'-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (2-fluoro-4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.38 mins MH^+ 369.

Example 33: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-cyano-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-cyanophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.21 mins MH^+ 362.

Example 34: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [4'-(methyloxy)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, [4-(methyloxy)phenyl]boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.29 mins MH^+ 367.

Example 35: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [3'-(methyloxy)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, [3-(methyloxy)phenyl]boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.29 mins MH^+ 367.

Example 36: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-chloro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (2-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.33 mins MH^+ 371.

Example 37: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [2'-(methyloxy)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, [2-(methyloxy)phenyl]boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-

bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.27 mins MH^+ 367.

Example 38: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-chloro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (4-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.39 mins MH^+ 371.

Example 39: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.39 mins MH^+ 371.

Example 40: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.42 mins MH^+ 389.

Example 41: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-4-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chloro-4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.78 mins MH^+ 403.

Example 42: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, phenylboronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.6 mins MH^+ 351.

Example 43: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [3'-chloro-4'-fluoro-5,6-bis(methyloxy)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, (3-chloro-4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-{[({[2-bromo-3,4-bis(methyloxy)phenyl]amino}carbonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.56 mins MH^+ 449.

Example 44: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-chloro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, phenylboronic acid and 1,1-dimethylethyl-(3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.71 mins MH^+ 371.

Example 45: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [3'-chloro-4'-fluoro-4-(methyloxy)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, (3-chloro-4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-{[({[2-bromo-5-(methyloxy)phenyl]amino}carbonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.71 mins MH^+ 419.

Example 46: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [4-(methyloxy)-2-biphenylyl]carbamate

According to the procedure outlined in example 10, phenylboronic acid and 1,1-dimethylethyl (3-*endo*)-{[({[2-bromo-5-(methyloxy)phenyl]amino}carbonyl) oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.54 mins MH^+ 367.

Example 47: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyloxy) methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.72 mins MH^+ 385.

Example 48: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-5-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chloro-4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.78 mins MH^+ 403.

Example 49: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (5-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, phenylboronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.59 mins MH^+ 351.

Example 50: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-3-methyl-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.6 mins MH^+ 385.

Example 51: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-fluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.74 mins MH^+ 389.

Example 52: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-fluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, phenylboronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.6 mins MH^+ 355.

Example 53: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4',6-difluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chloro-4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-3-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.72 mins MH^+ 407.

Example 54: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (6-fluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, phenylboronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-3-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.53 mins MH^+ 355.

Example 55: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4',5-difluoro-2-biphenylyl)carbamate

According to the procedure outlined in example 10, (3-chloro-4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.71 mins MH^+ 407.

Example 56: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [3'-chloro-4-(methyloxy)-2-biphenylyl]carbamate trifluoroacetate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-{[({[2-bromo-4-methyloxyphenyl]amino}carbonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.67 mins MH^+ 401.

Example 57: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl [4-(acetylamino)-3'-chloro-2-biphenylyl]carbamate trifluoroacetate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-{[({[5-(acetylamino)-2-bromophenyl]amino} carbonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.45 mins MH^+ 428.

Example 58: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-6-fluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-3-fluorophenyl)amino]carbonyl} oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.66 mins MH^+ 389.

Example 59: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-fluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 10, (3-chlorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl} oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.50 mins MH^+ 389.

Example 60: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate

A solution of 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl) amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (45 mg) and (3-fluorophenyl)boronic acid (21 mg) in dimethylformamide (0.75ml) was treated with triethylamine (42µl), tetrakis(triphenylphosphino)palladium (0) (58 mg) and water (0.25ml). The mixture was placed in a sealed reaction tube and heated in a microwave (CEM Explorer, 150°C, 10 minutes, pressure 250psi, power 100W). After cooling to room temperature, the solvent was removed under vacuum. The residue was dissolved in chloroform (1ml) then washed sequentially with 2N hydrochloric acid (0.5ml) and water (0.5ml). The organic phase was separated and the solvent was removed under vacuum. The residue was dissolved in acetonitrile (1ml) and treated with *p*-toluenesulfonic acid (20mg) . The resulting mixture was heated at reflux for 3 hours. After cooling to room temperature, the solution was purified by loading onto a SPE cartridge (SCX, 500mg) then washing with methanol and eluting with 2M ammonia in methanol. The solvent was removed under vacuum and the residue was purified by MDAP to afford the title compound (4.9 mg). LC/MS ESI R_T 2.63 mins MH^+ 369.

Example 61: (3-*endo*)- 8-azabicyclo[3.2.1]oct-3-ylmethyl (4-chloro-3'-fluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino] carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.72 mins MH^+ 389.

Example 62: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-fluoro-5-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.62 mins MH^+ 369.

Example 63: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-fluoro-3-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.50 mins MH^+ 369.

Example 64: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',4-difluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.63 mins MH^+ 373.

Example 65: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',5-difluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.55 mins MH^+ 373.

Example 66: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-3',4-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluoro-3-methylphenyl) boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl) amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.73 mins MH^+ 383.

Example 67: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-chloro-4'-fluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluoro-3-methylphenyl) boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino] carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.8 mins MH^+ 403.

Example 68: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-3',5-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluoro-3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.72 mins MH^+ 383.

Example 69: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-3,3'-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluoro-3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.59 mins MH^+ 383.

Example 70: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4,4'-difluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluoro-3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.72 mins MH^+ 387.

Example 71: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4',5-difluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluoro-3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.65 mins MH^+ 387.

Example 72: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',4-dichloro-4'-fluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-chloro-4-fluorophenyl) boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl) amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.81 mins MH^+ 423.

Example 73: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4'-fluoro-3-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-chloro-4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.63 mins MH^+ 403.

Example 74: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4,4'-difluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-chloro-4-fluorophenyl) boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino] carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.72 mins MH^+ 407.

Example 75: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (2-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl)amino] carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.59 mins MH^+ 369.

Example 76: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-chloro-2'-fluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (2-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.66 mins MH^+ 389.

Example 77: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-5-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (2-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.57 mins MH^+ 369.

Example 78: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2'-fluoro-3-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (2-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.46 mins MH^+ 369.

Example 79: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (2',5-difluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (2-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.62 mins MH^+ 369.

Example 80: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-4-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.62 mins MH^+ 369.

Example 81: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-chloro-4'-fluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.70 mins MH^+ 389.

Example 82: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-5-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.62 mins MH^+ 369.

Example 83: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4'-fluoro-3-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.48 mins MH^+ 369.

Example 84: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4,4'-difluoro-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-fluorophenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.62 mins MH^+ 373.

Example 85: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',4-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.7 mins MH^+ 365.

Example 86: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-chloro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.78 mins MH^+ 385.

Example 87: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3',5-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.68 mins MH^+ 365.

Example 88: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3,3'-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.55 mins MH^+ 365.

Example 89: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-fluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.70 mins MH^+ 369.

Example 90: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (5-fluoro-3'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (3-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.62 mins MH^+ 369.

Example 91: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4,4'-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.71 mins MH^+ 365.

Example 92: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-chloro-4'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-chlorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.79 mins MH^+ 385.

Example 93: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4',5-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.70 mins MH^+ 365.

Example 94: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3,4'-dimethyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-6-methylphenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.55 mins MH^+ 365.

Example 95: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (4-fluoro-4'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-5-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.70 mins MH^+ 369.

Example 96: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (5-fluoro-4'-methyl-2-biphenylyl)carbamate trifluoroacetate

According to the procedure outlined in example 60, (4-methylphenyl)boronic acid and 1,1-dimethylethyl (3-*endo*)-[({[(2-bromo-4-fluorophenyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate were reacted to generate the title compound. LC/MS ESI R_T 2.64 mins MH^+ 369.

Example 97: (3-*endo*)-[({[(3'-chloro-4-fluoro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate

A solution of (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-4-fluoro-2-biphenylyl)carbamate (47mg) in DMF (1ml) was treated with potassium carbonate (17mg) and methyl iodide (30ul). After 16h the solvent was evaporated and the residue purified by MDAP to give the title compound. LC/MS ESI R_T 2.55 mins MH^+ 417.

Example 98: (3-*endo*)-[({[(3'-chloro-5-hydroxy-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate

The title compound was prepared from (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-hydroxy-2-biphenylyl)carbamate according to the procedure outlined in example 97. LC/MS ESI R_T 2.22 mins MH^+ 415.

Example 99: (3-*endo*)-[({[(3'-chloro-3-methyl-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate

The title compound was prepared from (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-3-methyl-2-biphenylyl)carbamate according to the procedure outlined in example 97. LC/MS ESI R_T 2.45 mins MH^+ 413.

Example 100: (3-*endo*)-[({[(3'-chloro-6-fluoro-2-biphenylyl)(methyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate

The title compound was prepared from (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-6-fluoro-2-biphenylyl)carbamate according to the procedure outlined in example 97. LC/MS ESI R_T 2.51 mins MH^+ 431.

Example 101: (3-*endo*)-[({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate

The title compound was prepared from (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-5-fluoro-2-biphenylyl)carbamate according to the procedure outlined in example 97. LC/MS ESI R_T 2.47 mins MH^+ 417.

Example 102: (3-*endo*)-[({[(3'-chloro-3-fluoro-2-biphenylyl)(methyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate

The title compound was prepared (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-3-fluoro-2-biphenylyl)carbamate according to the procedure outlined in example 97. LC/MS ESI R_T 2.54 mins MH^+ 431.

Example 103: (3-*endo*)-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane trifluoroacetate

The title compound was prepared from (3-*endo*)-bicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate according to the procedure outlined in example 97. LC/MS ESI R_T 2.45 mins MH^+ 400.

Example 104: (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl 2-biphenylylcarbamate

A mixture of 1,1-dimethylethyl -(3-*endo*)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (162 mg) and 2-isocyanato-biphenyl (130.7 mg) in DMF (2 ml) was stirred at room temperature for 1 hour. The reaction mixture was purified directly by Gilson preparatory HPLC to give (3-*endo*)-3-(biphenyl-2-ylcarbamoyloxymethyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (190 mg, 65%), which was dissolved in 12 ml of methylene chloride and 3 ml of TFA. The above mixture was heated at 65°C for 2 hours, concentrated and redissoved in ethyl acetate (30 ml). The organic phase was washed with 1 N sodium hydroxide (10 ml). The aqueous phase was extracted with ethyl acetate (3 X 10 ml).

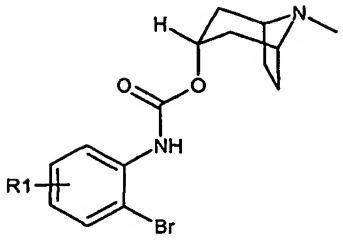
The combined organics were washed with brine (10 ml) and dried over Na_2SO_4 to give the title compound (98 mg, 75%). LC/MS ESI R_T 1.62min M^+ 337

Intermediate 17: 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromophenyl)carbamate

A solution of 2-bromobenzoic acid (1.00 g, 5.00 mmol) in THF (10 mL) was added to a Radleys® Carousel Reaction tube fitted with magnetic stirring bar. Diphenylphoshine azide (1.18 mL, 5.50 mmol) was then added, followed by ethylamine (1.40 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 10 minutes, and 8-methyl-8-azabicyclo[3.2.1]octan-3-ol (1.19 g, 7.50 mmol) was then added. Stirring continued for 16 h at 75 °C, and the precipitated phosphonic acid was removed by vacuum filtration. The filtrate was then concentrated under reduced pressure. The residue was dissolved in DCM (6 ml), and the solution was transferred to a 10 mL hydrophobic frit that contained H_2O (3 mL). The aqueous layer was extracted with DCM (1 x 4 mL), and the combined organic layers were diluted with 50 mL of DCM. This solution was loaded onto a 10 g normal phase aminopropyl SPE cartridge primed with 60 mL of DCM. The cartridge was then sequentially eluted with DCM (1 x 60 mL), Et_2O (1 x 60 mL), EtOAc (5 x 60 mL), and MeOH (1 x 60 mL). The title compound was found in the EtOAc fractions, which were concentrated under reduced pressure to yield the title compound 0.309 g (18%). LC/MS ESI R_T 1.44 min, MH^+ 339.

The following intermediates in Table 1 were prepared according to the procedure outlined for intermediate 17.

Table 1



Intermediate	R1	MS [M+H]	R_t (min)
18	5-fluoro	358	1.54
19	6-methyl	354	1.32
20	4-methyl	354	1.44
21	4-fluoro	358	1.39
22	5-methyl	354	1.46
23	5-chloro	374	1.51
24	4-chloro	374	1.43
25	6-fluoro	358	1.28
26	3-fluoro	358	1.45

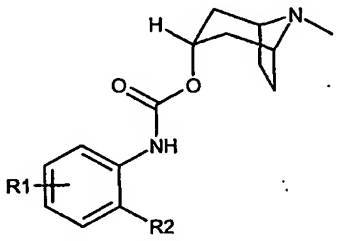
Example 105: 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4-fluoro-2-biphenylyl)carbamate

PS-PPh_3-Pd (0.020 g, 0.0026 mmol) was added to a solution of 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromo-5-fluorophenyl)carbamate (0.063 g, 0.18 mmol) in DME (1 mL) in a 4 mL glass vial. A solution of 3-chlorophenyl boronic acid (0.055 g, 0.35 mmol) in EtOH (1 mL) was added to the reaction mixture, followed by a solution of K_2CO_3 (0.056 g, 0.41 mmol) in H_2O (0.5 mL). The glass vial was capped, and the reaction was agitated in an Innova® Shaker at 80 °C for 48 h. The resin was removed by gravity filtration, washed with DME (1 x 1 mL) and EtOH (1 x 1 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (4 mL) and transferred onto a 6 mL hydrophobic frit. H_2O (2 mL) was added to the solution and mixed to remove base. The layers were

separated, and the aqueous layer was washed with DCM (1 x 4 mL). The combined organic layers were concentrated under reduced pressure and purified by Gilson® preparatory HPLC to yield the title compound (0.030 g, 43%). LC/MS ESI R_T 1.73 min, MH^+ 389.

The following examples in Table 2 were prepared according to the procedure outlined in Example 105.

Table 2



Example	R1	R2	MS [M+H]	R_t (min)
106	4-fluoro	phenyl	355	1.61
107	4-fluoro	3-chloro-4-fluoro-phenyl	407	1.69

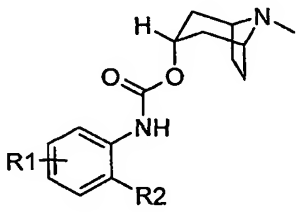
Example 108: 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-4'-fluoro-2-biphenylyl)carbamate

PS-PPh_3-Pd (0.020 g, 0.0026 mmol) was added to a solution of 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromo-5-chlorophenyl)carbamate (0.035 g, 0.095 mmol) in DME (1 mL) in a microwave reactor tube. A solution of 3-chlorophenyl boronic acid (0.030 g, 0.19 mmol) in EtOH (1 mL) was added to the reaction mixture, followed by a solution of K_2CO_3 (0.030 g, 0.22 mmol) in H_2O (0.5 mL). The reaction vial was capped and heated at 165° C for 10 min. The resin was removed by gravity filtration, washed with DME (1 x 1 mL) and EtOH (1 x 1 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (4 mL) and transferred onto a 6 mL hydrophobic frit. H_2O (2.0

mL) was added to the solution and mixed to remove base. The layers were separated, and the aqueous layer was washed with DCM (1 x 4 mL). The combined organic layers were concentrated under reduced pressure and purified by Gilson® preparatory HPLC to yield the title compound (0.021 g, 54%). LC/MS ESI R_T 1.76 min, MH^+ 405

The following examples in Table 3 were prepared according to the procedure outlined in Example 108.

Table 3



Example	R1	R2	MS [M+H]	R_t (min)
109	4-chloro	3-chloro-4-fluoro phenyl	423	1.89
110	4-chloro	Phenyl	371	1.49

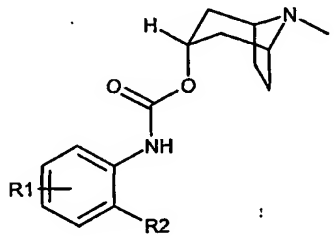
Example 111: Preparation of 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-2-biphenylyl)carbamate

$Pd(PPh_3)_4$ (0.089 g, 0.077 mmol) was added to a solution of 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromophenyl)carbamate (0.130 g, 0.383 mmol) in DME (1 mL) in a 4 mL glass vial with a magnetic stir bar. A solution of 3-chlorophenylboronic acid (0.090 g, 0.58 mmol) in EtOH (1 mL) was added to the reaction mixture, followed by a solution of K_2CO_3 (0.200 g, 1.44 mmol) in H_2O (0.5 mL). The glass vial was capped and heated at 80° C for 16 h. The reaction mixture was concentrated under reduced pressure, taken up in DCM (4 mL), and transferred onto a 6 mL hydrophobic frit. H_2O (2 mL) was added to the solution

and mixed to remove base. The layers were separated, and the aqueous layer was washed with DCM (1 x 4 mL). The combined organic layers were concentrated under reduced pressure and purified by Gilson® preparatory HPLC to yield the title compound (0.042 g, 30%). LC/MS ESI R_T 1.74 min, MH^+ 371.

The following examples in Table 4 were prepared according to the procedure outlined in Example 111.

Table 4



Example	R1	R2	MS [M+H]	R_t (min)
112	3-fluoro	phenyl	355	1.29
113	3-fluoro	3-chlorophenyl	389	1.34
114	3-fluoro	3-chloro-4-fluoro-phenyl	407	1.41
115	6-fluoro	phenyl	355	1.14
116	6-fluoro	3-chloro-4-fluoro-phenyl	407	1.30

Example 117: 3-{[(2-biphenylylamino)carbonyl]oxy}-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

First step

$Pd(PPh_3)_4$ (0.089 g, 0.077 mmol) was added to a solution of 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromophenyl)carbamate (0.060 g, 0.177 mmol) in DME (1 mL) in a 4 mL glass vial with a magnetic stir bar . A solution of phenylboronic acid (0.043 g, 0.354 mmol) in EtOH (1 mL) was added to the reaction mixture, followed by a solution of K_2CO_3 (0.056 g, 0.407 mmol) in H_2O (0.5 mL).

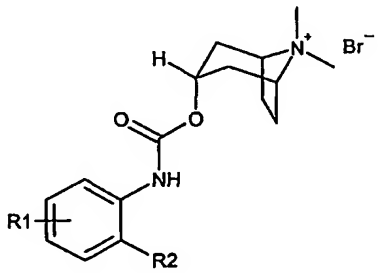
The glass vial was capped and heated at 80° C for 16 h. The reaction mixture was concentrated under reduced pressure, taken up in DCM (4 mL), and transferred onto a 6 mL hydrophobic frit. H_2O (2 mL) was added to the solution and mixed to remove base. The layers were separated, and the aqueous layer was washed with DCM (1 x 4 mL). The combined organic layers were concentrated under reduced pressure and purified by Gilson preparatory HPLC to yield 8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-biphenylylcarbamate (0.050 g, 83%). LC/MS ESI R_T 1.54 min, MH^+ 337.

Second step

A 2 M solution of MeBr in *tert*-butyl methyl ether (0.700 mL, 1.49 mmol) was added to a solution of 8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-biphenylylcarbamate (0.050 g, 0.15 mmol) in a mixture (1:1) of DCM/CH_3CN (2 mL) in a glass vial with a magnetic stirring bar under argon. The reaction was stirred at room temperature for 16 h. The solvent was evaporated, and the product was dried under high vacuum to yield the title compound (0.050 g, 94%). LC/MS ESI R_T 1.72 min, MH^+ 351

The following examples in Table 5 were prepared according to the procedure outlined in Example 117 reacting the appropriate boronic acid and bromo-phenyl intermediates.

Table 6



Example	R1	R2	MS [M+]	R_t (min)
118	6-fluoro	3-chlorophenyl	403	1.72
119	3-fluoro	phenyl	369	1.38
120	3-fluoro	3-chlorophenyl	403	1.53
121	3-fluoro	3-chloro-4-phenyl	420	1.79
122	5-fluoro	3-chlorophenyl	403	1.80
123	6-fluoro	phenyl	369	1.33
124	6-fluoro	3-chloro-4-phenyl	421	1.53
125	5-chloro	3-chlorophenyl	420[a]	1.97
126	6-methyl	phenyl	365	1.37
127	6-methyl	3-chlorophenyl	399	1.81
128	4-chloro	phenyl	385[a]	1.53
129	4-chloro	3-chloro-4-phenyl	438[a]	1.47
130	4-methyl	3-chlorophenyl	399	1.89
131	5-methyl	phenyl	365	1.47
132	5-methyl	3-chloro-4-fluoro	417	1.87
133	5-methyl	3-chlorophenyl	399	1.86
134	H	3-chloro-4-fluoro phenyl	403	1.86

[a] [M+1-CH_3]

Example 135: 3-({[(3',5-dichloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

Following the procedure outlined in Example 117, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromo-4-chlorophenyl)carbamate was reacted sequentially with 3-chlorophenyl boronic acid and MeBr to give the title compound (6.7 mg). NMR (CD_3OD, 400 MHz; δ): 1.92 ppm (d, 2H), 2.30-2.39 ppm (m, 4H), 2.80 ppm (d, 2H), 3.13 ppm (s, 3H), 3.18 ppm (s, 3H), 3.85-3.88 ppm (m, 2H), 7.35-7.49 ppm (comp, 8H).

Example 136: 3-({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

Following the procedure outlined in the 2nd step of Example 117, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (3'-chloro-2-biphenylyl)carbamate was reacted with MeBr to give the title compound (43.7 mg). NMR (DMSO, 400 MHz; δ): 1.69 ppm (d, 2H), 2.08-2.25 ppm (m, 4H), 2.45 ppm (d, 2H), 3.01 ppm (s, 3H), 3.08 ppm (s, 3H), 3.81 ppm (m, 2H), 4.75 ppm (t, 1H), 7.35-7.49 ppm (comp, 8H), 9.06 ppm (s, 1H).

Example 137: 3-({[(3'-chloro-4',5-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

Preparation of (3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromo-4-fluorophenyl)carbamate

A solution of 2-bromo-4-fluorobenzoic acid (1.09 g, 5.00 mmol) in THF (10 mL) was added to a carousel reaction tube fitted with magnetic stirring bar. Diphenylphoshine azide (1.18 mL, 5.50 mmol) was then added, followed by ethylamine (1.40 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 10 minutes, and 8-methyl-8-azabicyclo[3.2.1]octan-3-ol (1.19 g, 7.50 mmol) was then added. Stirring continued for 16 h at 75 °C, and the precipitated phosphonic acid was removed by vacuum filtration. The filtrate was then concentrated under reduced pressure. The residue was dissolved in DCM (6 ml), and the solution was transferred to a 10 mL hydrophobic frit that contained H_2O (3 mL). The aqueous layer was extracted with DCM (1 x 4 mL), and the combined organic layers were diluted with 50 mL of DCM. This solution was loaded onto a 10 g aminopropyl SPE cartridge primed with 60 mL of DCM. The cartridge was then sequentially eluted with DCM (1 x 60 mL), Et_2O (1 x 60 mL), EtOAc (5 x 60 mL), and MeOH (1 x 60 mL). The title compound was found in the EtOAc fractions, which were concentrated under reduced pressure to yield (3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromo-4-fluorophenyl)carbamate (0.343 g). LC/MS ESI R_T 1.39 min, MH^+ 358.

Preparation of 3-({[(3'-chloro-4',5-difluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

PS-PPh_3-Pd (0.020 g, 0.0026 mmol) was added to a solution of (3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromo-4-fluorophenyl)carbamate (0.068 g, 0.19 mmol) in DME (1 mL) in a 4 mL glass vial. A solution of 3-chloro4-fluorophenyl boronic acid (0.066 g, 0.38 mmol) in EtOH (1 mL) was added to the reaction mixture, followed by a solution of K_2CO_3 (0.056 g, 0.41 mmol) in H_2O (0.5 mL). The glass vial was capped, and the reaction was agitated in an shaker at 80 °C for 48 h. The resin was removed by gravity filtration, washed with DME (1 x 1 mL) and EtOH (1 x 1 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (4 mL) and transferred onto a 6 mL hydrophobic frit. H_2O (2 mL) was added to the solution and mixed to remove base. The layers were separated, and the aqueous layer was washed with DCM (1 x 4 mL). The combined organic layers were concentrated under reduced pressure and purified by Gilson® preparatory HPLC to yield an oil which was treated with a solution of 2 M solution of MeBr in *tert*-butyl methyl ether (0.700 mL, 1.49 mmol) in a mixture (1:1) of DCM/CH_3CN (2 mL) in a glass vial with a magnetic stirring bar under argon. The resulting mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the product was dried under high vacuum to yield the title compound (0.437 mg). NMR (DMSO, 400 MHz; δ): 1.69 ppm (d, 2H), 2.10-2.40 ppm (m, 4H), 2.45 ppm (d, 2H), 3.02 ppm (s, 3H), 3.08 ppm (s, 3H), 3.81 ppm (m, 2H), 4.75 ppm (t, 1H), 7.27-7.52 ppm (comp, 6H), 9.06 ppm (s, 1H).

Example 138: 3-({[(3'-chloro-5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

Following the procedure outlined in Example 117, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2-bromo-4-fluorophenyl)carbamate was reacted sequentially with 3-chlorophenyl boronic acid and MeBr to give the title compound (31.2 mg). NMR (DMSO, 400 MHz; δ): 1.75 ppm (d, 2H), 2.08-2.45 ppm (m, 4H), 2.46 ppm (d, 2H), 3.01 ppm (s, 3H), 3.09 ppm (s, 3H), 3.81 ppm (m, 2H), 4.79 ppm (t, 1H), 7.19 ppm (t, 1H), 7.19-7.49 ppm (comp, 6H), 9.16 ppm (s, 1H).

Example 139: 3-({[(5-fluoro-2-biphenylyl)amino]carbonyl}oxy)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

Following the procedure outlined in the 2nd step of Example 117, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl (5-fluoro-2-biphenylyl)carbamate was reacted with MeBr to give the title compound (43.7 mg). NMR (DMSO, 400 MHz; δ): 1.68 ppm (d, 2H), 2.10-2.45 ppm (m, 4H), 2.46 ppm (d, 2H), 3.00 ppm (s, 3H), 3.07 ppm (s, 3H), 3.78 ppm (m, 2H), 4.70 ppm (t, 1H), 7.23 ppm (t, 1H), 7.39-7.43 ppm (comp, 8H), 8.95 ppm (s, 1H).

Example 140: (3-*endo*)-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

Preparation of 1,1-dimethylethyl 3-(*endo*)-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate

A solution of the commercially available 3'chlorbiphenylcarboxylic acid (500 mg, 2.15 mmol) in THF (20 ml) was treated with diphenylphosphoryl azide (508 µl), triethylamine (620 µl) and 1,1-dimethylethyl -(3-*endo*)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (622 mg). The reaction mixture was heated at reflux for 12 hours, cooled to room temperature, diluted with ethyl acetate and washed sequentially with 0.5N aqueous HCl, sat $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$, filtered and evaporated to give a crude oil which was purified by flash chromatography. Elution with a ethyl acetate/hexane 1:3 mixture afforded 1,1-dimethylethyl 3-(*endo*)-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate as an oil (904 mg). LC/MS ESI R_T 2. 97 mins.

Preparation of (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate hydrochloride

A mixture of 1,1-dimethylethyl 3-(*endo*)-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (904 mg) and 1HCl in ether (10 ml) in methanol (5 ml) was allowed to stir at room

temperature for 12 hours. The solvents were evaporated under vacuum. The resulting residue was redisolved in water (50 ml) then washed with ether (2 X 100 ml), basified to pH 13 with 2.5 N aq. NaOH (10 ml) then extracted with ethyl acetate (3 X 100 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated under vacuum to give (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate hydrochloride as a white solid (550 mg). LC/MS ESI R_T 1.83 mins MH^+ 371.

Preparation of [(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]methyl (3'-chloro-2-biphenylyl)carbamate

A solution of $NaBH_4$ (20.4 mg) was added to a mixture of (3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate hydrochloride (100 mg, 0.27 mmol) and formaldehyde (102.6 µl, 37% in water, 10.8 mmol) in methanol (5 ml). The resulting solution was allowed to stir at room temperature for 48 hours. More formaldehyde (100 µl) and $NaBH_4$ (20 mg) were added to the reaction mixture. After 12 hours of stirring at room temperature, the solvents were evaporated under vacuum to give a residue which was partitioned between DCM (6 ml) and water (6 ml). The organic layer was separated and loaded onto a 2g NH_2 SPE cartridge and sequentially eluted with DCM (3 x 5ml), ethyl acetate (2 X 5 ml) and methanol (2 X 5 ml). The last DCM fraction and the two ethyl acetate fractions were combined and evaporated to give (3-*endo*)-bicyclo[3.2.1]oct-3-ylmethyl (3'-chloro-2-biphenylyl)carbamate as a white solid (70 mg). LC/MS ESI R_T 1.92 mins M^+ 385.

Preparation of (3-*endo*)-[({[(3'-chloro-2-biphenylyl)amino]carbonyl}oxy)methyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide

A solution of [(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]methyl (3'-chloro-2-biphenylyl)carbamate (48 mg) in DMF (2 ml) and acetonitrile (2 ml) was treated with methyl bromide (50 µl of a 2M solution in t-butyl ethyl ether). After stirring at room temperature for 12h the solvents were evaporated under vacuum to give the title compound (57 mg). LC/MS ESI R_T 1.81 mins M^+ 399.

The compounds of the present invention exhibit IC50 values of 1.5μM or less.

Abbreviations

BOC	*tert*-butyloxycarbonyl
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
ESI	Electrospray ionization
HPLC	High pressure liquid chromatography
LC/MS	Liquid chromatography/Mass spectrometry
MDAP	Mass directed automated preparative
Rt	Retention time
SPE	Solid phase extraction
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* functional assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described (H. M.Sarau *et al*, 1999. *Mol. Pharmacol.* 56, 657-663). CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 μl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 μM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then

aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels. The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction – potency and duration of action

Airway responsiveness to methacholine was determined in awake, unrestrained Balb C mice ($n = 6$ each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine(2). Mice were pre-treated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally (i.n.) and were then placed in the plethysmography chamber a given amount of time following drug administration (15 min – 96 h). For potency determination, a dose response to a given drug was performed, and all measurements were taken 15 min following i.n. drug administration. For duration of action determination, measurements were taken anywhere from 15 min to 96 hours following i.n. drug administration.

Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with

an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software. This experiment allows the determination of duration of activity of the administered compound.

The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis.

FORMULATION-ADMINISTRATION

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative (e.g., salts and esters) thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. The present invention may be used to treat a mammal, including a human, in need of treatment.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

Compounds of formula (I) will be administered via inhalation via the mouth or nose.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di- or poly-saccharides (e.g., lactose or starch), organic or inorganic salts (e.g., calcium chloride, calcium phosphate or sodium chloride), polyalcohols (e.g., mannitol), or mixtures thereof, alternatively with one or more additional materials, such additives included in the blend formulation to improve

chemical and/or physical stability or performance of the formulation, as discussed below, or mixtures thereof. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients, or may be formed into particles comprising the compound, optionally other therapeutically active materials, and excipient materials, such as by co-precipitation or coating.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant as an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup or perforated plate, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula

(I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disk-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. US Patents Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose

of medicament upon each actuation by means of the valve, which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum aerodynamic particle size for inhalation into the bronchial system for localized delivery to the lung is usually 1-10μm, preferably 2-5μm. The optimum aerodynamic particle size for inhalation into the alveolar region for achieving systemic delivery to the lung is approximately .5-3 μm, preferably 1-3 μm. Particles having an aerodynamic size above 20μm are generally too large when inhaled to reach the small airways. Average aerodynamic particle size of a formulation may be measured by, for example cascade impaction. Average geometric particle size may be measured, for example by laser diffraction, optical means.

To achieve a desired particle size, the particles of the active ingredient as produced may be size reduced by conventional means eg by controlled

crystallization, micronisation or nanomilling .The desired fraction may be separated out by air classification. Alternatively, particles of the desired size may be directly produced, for example by spray drying, controlling the spray drying parameters to generate particles of the desired size range. Preferably, the particles will be crystalline, although amorphous material may also be employed where desirable. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention, such that the "coarse" carrier is non-respirable. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm. Additive materials in a dry powder blend in addition to the carrier may be either respirable, i.e., aerodynamically less than 10 microns, or non-respirable, i.e., aerodynamically greater than 10 microns.

Suitable additive materials which may be employed include amino acids, such as leucine; water soluble or water insoluble, natural or synthetic surfactants, such as lecithin (e.g., soya lecithin) and solid state fatty acids (e.g., lauric, palmitic, and stearic acids) and derivatives thereof (such as salts and esters); phosphatidylcholines; sugar esters. Additive materials may also include colorants, taste masking agents (e.g., saccharine), anti-static-agents, lubricants (see, for example, Published PCT Patent Appl. No. WO 87/905213, the teachings of which are incorporated by reference herein), chemical stabilizers, buffers, preservatives, absorption enhancers, and other materials known to those of ordinary skill.

Sustained release coating materials (e.g., stearic acid or polymers, e.g. polyvinyl pyrolidone, polylactic acid) may also be employed on active material or active material containing particles (see, for example, Patent Nos. US 3,634,582, GB 1,230,087, GB 1,381,872, the teachings of which are incorporated by reference herein).

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity

adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Preferred unit dosage formulations are those containing an effective dose, as herein before recited, or an appropriate fraction thereof, of the active ingredient.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.